REMARKS

Claim 92 has been amended to provide antecedent basis as suggested by the Examiner. A new title is provided that conforms to the pending claims. Applicants now turn to the specific comments in the office action.

35 U.S.C. § 112, second paragraph

The rejection of claim 92 has been addressed as discussed above.

35 U.S.C. § 102

Claims 90-92, 94, 96 and 97 stand rejected as allegedly anticipated by Brazil, which is alleged to have an electronic publication date of April 5, 2000[1]. Brazil is alleged to teach contacting microaggregates of Aβ with an antibody to Aβ and microglial cells and determining uptake of Aβ into the microglial cells.

In reply, applicants attach a declaration under 37 C.F.R. § 1.131, which establishes that they had completed our invention as recited in claim 90, and in particular so much of the invention as might be alleged to be disclosed or suggested by Brazil *et al.* before the publication date of Brazil *et al.* The provision of the declaration should not be construed as acquiescence in the merits of the rejection. In brief, the declaration summarizes an experiment described in attached notebook pages, which tests the ability of the monoclonal antibody 10D5 to clear amyloid deposits from a transgenic mouse model. In the experiment, 10D5 was combined with the amyloid deposit and then microglial cells in comparison with a control mixture of amyloid deposit and microglial cells without antibody. After incubation and staining with a labeled 3D6 antibody, a series of microscopic measurements was made to monitor reduction in the amount of amyloid deposit in the medium. The increased punctuate staining in the 10D5 sample relative to the control indicated that more clearing activity was occurring in the treated

[1] Applicants note that the cover page of Brazil actually refers to a date of March 23, 2000, and use this date for purposes of the attached 131 declaration only. Applicants reserve the right to revisit the issue regarding the actual publication date should this be relevant in this or other proceedings.

sample than the control. It was concluded that 10D5 had clearing activity against the amyloid deposit.

The above experiment contains all of the steps required by claim 90 and thus establishes reduction to practice of claim 90. The same is true for each dependent claim. The experiment includes monitoring the amount of an antigen associated with the deposit (*i.e.*, Aβ) as recited by claim 91, combining the amyloid deposit and antibody before adding microglial cells (claim 92), an amyloid deposit from an animal having Alzheimer's pathology (claims 93 and 100), the antigen is Aβ (claim 94), microscopic monitoring (claim 96), a monoclonal antibody, *i.e.*, 10D5 (claim 97), an epitope within residues 1-7 of Aβ, *i.e.*, 10D5 (claim 98). The experiment also discloses at least as much of the claim invention as is asserted to be disclosed or suggested by Brazil.

For these reasons, withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103

Claims 90-94, 96-98 and 100 stand rejected as allegedly obvious over Brazil in view of DeWitt and Alan Solomon, WO 99/60024, further in view of Johnson-Wood, Friedland, and Walker.

This rejection is respectfully traversed. In view of the 131 declaration, Brazil is not prior art. In the absence of the primary reference, no prima facie case of obviousness has been established. Applicants disagree with the combination of Brazil with the various secondary references, but in view of the removal of Brazil as prior art, do not address the combinations at this time.

Claims 90-94, 96-98 and 100 are rejected as obvious over Vitek as evidenced by Benjamini in view of DeWitt and Alan Solomon WO 99/60024 (Solomon) in further view of Johnson-Wood, Friedland and Walker. Vitek is alleged to teach an in vitro assay used for determining the ability of agents to modulate clearance of AGE-modified insoluble Aβ by incubation with cultured phagocytic cells. Benjamini is alleged to teach that opsonization of particles by antibodies and ADCC are important mechanism for clearing potentially harmful

substances. The Examiner acknowledges Vitek does not teach using tissue samples from the brain of an Alzheimer's patients or an animal having pathology or screening for monoclonal antibodies that bind to an epitope within Aβ1-7. DeWitt is alleged to teach measuring microglial cell's capacity to phagocytose senile plaques from Alzheimer's patients. Alan Solomon is alleged to teach methods of amyloid removal using anti-amyloid antibodies that enhance the cell-mediated immune response to deposits of amyloid. Johnson-Wood, Friedland and Walker are all cited as suggesting that the N-terminus of Aβ is an epitope accessible for binding of antibodies on the surface of amyloid plaques. The Examiner alleges that Walker proposes that monoclonal antibodies such as 10D5 are particularly valuable for diagnostic techniques as well as for potential therapeutic applications. Applicants respectfully traverse.

The subject of what Vitek discloses alone or as further evidenced by Benjamini has been extensively discussed in previous responses and in particular at pp. 5-9 of the response filed February 6, 2006. It is unfortunate that the present Examiner has not commented on the distinctions pointed out in this response. In brief, Vitek's method differs from that claimed in at least two respects (1) Vitek does not disclose simultaneous presence of an antibody and phagocytic cells in an in vitro clearing assay and (2) Vitek does not disclose that the clearing reaction screens an antibody for clearing activity. Although Vitek discusses various methods of treatment and diagnosis, only a small portion of the patent relates to an *in vitro* assay for phagocytosis at col. 22, lines 54-66. As discussed in the last response and reiterated below, the assay discussed at col. 22, lines 54-66 is not the same as that claimed. In Vitek's *in vitro* assay, the object is not to screen an antibody but rather to screen AGE-TF (thioflavin) for capacity to modify insoluble or aggregated Aβ (col. 22, lines 53-55). This is achieved by the following steps. First, AGE-TF is contacted with aggregated Aβ. The incorporation of AGE-TF into aggregated Aβ is then tested by ELISA using an antibody (col. 22, lines 58-61). The antibody in this step is used simply as a conventional diagnostic reagent, and is not itself being screened for anything. After verifying incorporation of AGE-TF, phagocytic cells are added to test for clearance of AGE-TF modified Aβ (col. 22, lines 61-65). However, at the time the phagocytic cells are added, there is no indication that the antibody used for the ELISA is still present. It would be most logical and typical practice when performing a diagnostic step on an intermediate

product in a process to perform the diagnostic step on only a sample of the intermediate so as to avoid influencing the further processing of the intermediate by contamination with the reagents in the diagnostic step. In any event, insofar as there is doubt as to whether Vitek proposes adding phagocytic cells to the same or a different vessel to that in which the ELISA using antibody to AGE-TF is performed, that doubt should inure to the benefit of applicants given that the burden of proof rests on the PTO (*In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984)).

Rather than simply repeating the rest of applicants' remarks from the previous response, which have not been addressed, applicants requestfully respect the Examiner to review these remarks in full at pp. 5-9 of the response of February 6, 2006. If the Examiner still disagrees she is requested to point out with specificity what disclosure of Vitek is being relied on for disclosure of simultaneous presence of an antibody and phagocytic cells in an in vitro clearing assay.

DeWitt an assay similar to that of Vitek, which suffers from the same deficiency. As in Vitek, DeWitt combines phagocytic cells and Aβ deposits but not antibodies. The object was to assess whether astrocytes can protect the Aβ deposits from the phagocytic cells. In both Vitek and DeWitt , the goal was to assess a role of microglial cells in clearing deposits and in neither reference is there any indication that antibodies were present in the respective assays.

In Solomon, the goal was similarly to assess the role of phagocytic cells "The involvement of a cellular component was demonstrated by in vitro neutrophil binding assays (see Figures 2A and 2B)..." (at p. 18, 3rd paragraph). Although Solomon reports combining deposits of lambda light chain with antibodies to lambda light chain and human neutrophil, he says nothing about screening the antibodies for clearing. Rather the goal was simply to understand mechanism by showing binding of human neutrophils to amyloid deposits. Thus, Solomon does not show that antibodies enhance clearance of Aβ deposits by phagocytic cells *in vitro*, much less suggest using such an enhancement as a screening assay.

In sum, each of Vitek, DeWitt and Alan Solomon is directed to assessing a role of phagocytic cells, and none of the references shows that antibodies enhance the effect of phagocytic cells alone on Aβ deposits *in vitro*, or proposes that such an enhancement should be

used to screen antibodies for therapeutic potential. Because these references suffer from similar deficiencies, it is respectfully submitted that they would not alone or in combination have rendered any of the present claims obvious.

The three remaining references, Johnson-Wood, Friedland and Walker are apparently cited against dependent claim 97 which recites an antibody binding within residues 1-7 of Aβ. Applicants disagree that the cited references would have motivated the skilled artisan to have selected an antibody with such a binding specificity for use in the claimed methods.

Johnson-Wood uses the 3D6 antibody to stain tissue sections from a transgenic mouse model. However, Johnson-Wood also used C-terminal antibodies to stain such tissue sections (see, g., p. 1533, second column). Because both N-terminal and C-terminal antibodies bound in such an assay, the reference does not provide any clear guidance for a preferred epitope specificity to achieve binding to plaques. Moreover, as is shown by the data in the present application (see Table 16 at p. 87), binding of an antibody to plaques does not necessarily imply that an antibody can clear plaques. Johnson-Wood provides no information at all about which antibody specificity, if any, is preferred for clearing plaques.

Walker reports that the 10D5 amyloid antibody binds to amyloid deposits, but does not suggest that such binding is related to a particular epitope specificity. Indeed, Walker characterizes the epitope specificity as Aβ 1-16 (p. 377, second column, third paragraph), a description that is general enough to include antibodies binding to over a third of the molecule. Walker also mentions the possibility of using antibodies as a vehicle to deliver other therapeutic agents to the brain. Such a possibility, even if realized, would have said nothing about the preferred epitope specificity for the antibody itself to induce a clearing response.

Friedland reports the 10D5 antibody binds to plaques. However, Friedland does not attribute the binding to any epitope specificity or even say explicitly what the antibody specificity of this antibody is. The only implicit indication is the statement that a 1-28 Aβ antigen was used for the generation of antibodies (p. 110, second column, last paragraph), but this description even if intended to apply to 10D5, is as general as to include epitopes covering about two thirds of the molecule. Like the other references, Friedland does not show that any

antibody clears amyloid deposits or otherwise provide guidance as a preferred epitope specificity for therapeutic use.

In sum, Johnson-Wood, Walker and Friedland indicate that antibodies to various parts of Aβ can bind to amyloid deposits, but do not identify a preferred epitope specificity for binding much less for clearing such deposits. For these reasons, it is respectfully submitted that claim 97 is distinguished on additional grounds.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-625-8100.

Respectfully submitted,

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